Aalto University
School of Chemical Technology

CHEM-E3225, Cell- and Tissue Engineering, 5 cr (2019)

TOPIC 1

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Introduction to Tissue Engineering

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(See Birla, Chapter 1: Introduction to Tissue Engineering

Nordström 2019

Tissue engineering

The interdisicplinary field that applies the principle of engineering and the life science towards the development of biological substitutes that restore and, maintain, or improve tissue function.

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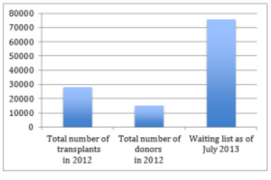
Problem with organ transplantations



Transplant situation in the U.S. in 2013, the data provided by Department of Health and Human Services; this situation is the same all over the world

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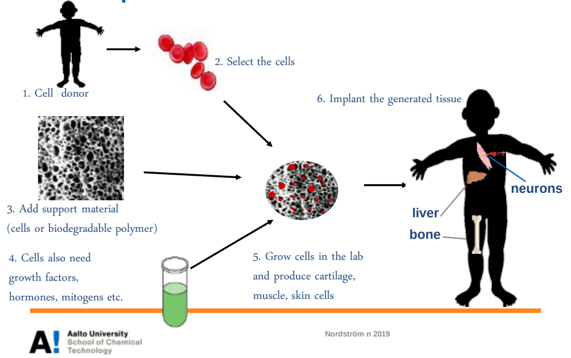
Nordström & Laakkonen
11.1. 2016

Tissue engineering and regenerative medicine

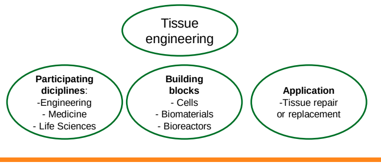
- Emerged in the mid-1990s
- The aim is to develop artificial tissue and organs
  - For therapeutic applications, the tissue is either grown in a patient or outside the patient and transplanted.
  - For diagnostic applications and pharmaceutical R&D, the tissue is made *in vitro* and used for testing drug metabolism and uptake, toxicity, and pathogenicity.
- The main tissue/organ groups:
  - Cardiovascular system
  - Musculoskeletal system
  - Urinary system
  - Airway system
  - Digestive system
  - Artificial skin
  - Central nervous system

What is a tissue engineered (TE) product ? The simple view



What is tissue engineering?

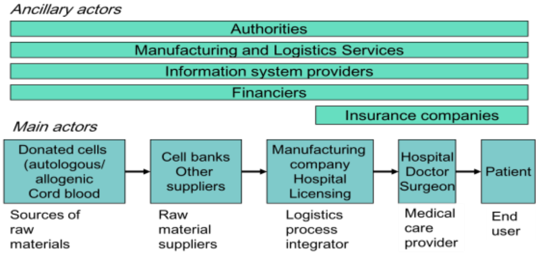
Reparative medicine, sometimes referred to as regenerative medicine or tissue engineering, is the regeneration and remodeling of tissue in vivo for the purpose of repairing, replacing, maintaining, or enhancing organ function, and the engineering and growing of functional tissue substitutes in vitro for implantation in vivo as a biological substitute for damaged or diseased tissues and organs. National Institute of Health, 2001



Cells + Biomaterials + Biomolecules = Tissue construct

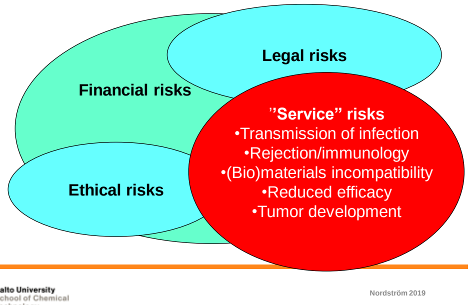
- Cells:
  - Autologous, allogeneic, and xenogeneic cells
  - Primary cells, stem cells, stem cell-derived cells
- Biomaterials:
  - Natural and synthetic biomaterials
  - Providing both physical and biochemical cues for cell growth, differentiation, and organization
- Biomolecules:
  - Growth factors, cytokines, and morphogens
- Engineering design:
  - 2D cell expansion
  - 3D tissue formation
  - Bioreactors
  - Vascularization

Supply chain for cells / tissues for regenerative medicine/tissue engineering



Nordström, K., Närhi, M. and Vepsäläinen A. (2009). Services for distribution of Tissue engineering products and therapies. *International Journal of Production and Productivity Management, vol 58, 1, 11-28.*

Risks involved with TE-products



Tissue engineering approaches

Three main approaches to tissue engineering:

1. to use isolated cells or cell substitutes as cellular replacement parts;
2. to use acellular materials (biomaterials or non-biomaterials) capable of inducing tissue regeneration;
3. to use a combination of cells and materials (typically in the form of scaffolds)

1. Cells as building blocks: Isolated cells or cell substitutes as cellular replacement parts

a) Living cells as building materials
- For example: Fibroblasts for skin replacement, chondrocytes for cartillage repair
- Undifferentiated stem cells

b) Autologous cells obtained from the same individual that receives the implantation

2. Biomaterials: Acellular materials capable of inducing tissue regeneration

These are bioengineered extracellular matrixes that enable diffusion of vital cell nutrients and allow
- Cell attachment and migration,
- Interaction between matrix and other cells
- Cell growth and differentiation

A biomaterial must be:
- Biocompatible
- Inert or bioactive
- Mechanically and chemically stable or biodegradable
- Manufacturable
- Sterilizable
- Non-thrombogenic if it has contact with blood

Types of biomaterials (continued)

1) Natural biomaterials:
- Derived from natural sources, e.g. purified protein components from animal tissues
- Have ability for biological recognition (as they are proteins and bild with cellular receptors and molecules – we will come back to this)
- There are concerns about complex purification, immunogenicity and pathogen transmission

2) Synthetic biomaterials:
- Great diversity and reproducibility
- Not animal product
- Do not have ability to interact with cells – are inert; Need to be equipped with molecular cues mimicking the natural cellular microenvironment = "functionalized" biomaterials

3. Scaffolds: Combination of cells and materials

- Cells can be seeded onto an artificial structure = scaffold
- Scaffolds support 3D growth of cells & formation of tissues

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  - Vascularization

Eight steps to tissue fabrication – what is needed ?

1. Cell sourcing (Identification, isolation, purification, expansion and characterizationof suitable cell source)
2. Biomaterial synthesis (Biomaterials provide support and extracellular matrix for cells)
3. Genetic manipulation (modification and fuctionalization of cells)
4. Scaffold cellularization (3D-scaffolds allow functional integration of cells to the interface)
5. Embedded sensors (monitor the tissue development and maturation)
6. Bioreactors (controlled physiological to guide the development of artificial tissue)
7. Vascularization (supports the metabolic activity of 3D artificial tissue)
8. *In vivo* assesment (test the functional performance of artificial tissue)

Challenges in tissue engineering

- The progress has been slow because of the lack of the comprehensive understanding of disease mechanisms
- More research is needed for *in vitro* and *in vivo* methods in cell in all the steps of tissue engineering to meet the high expectations of artificial tissue constructs
- Also the assessment of the artificial tissue needs to be efficient and standardized
- Regulatory (=legal) requirements have developed alongside product development and therefore difficult to predict what requirements are to be fulfilled for an individual product to pass requirement for safety and efficacy and become an approved commercial product

Scientific challenges in Tissue Engineering (Birla 2014, figure 1.6.) 1/2

Cel Sourcing
Where will the cells come fromm ?
If using stem cells, what differentiation strategy will be used ?

Biomaterial synthesis
What biomaterial will be used ?
What are the mechanical/ physical/ chemical etc. Properties ?

Genetic manipulation
Which genes can be manipulated ?
Are there risks of mutagenesis and random insertions ?

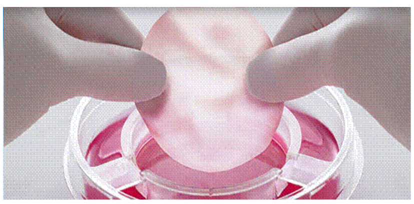
Scaffold vascularization
What will be the degree of cell/matrix interction ?
Is the functional coupling between cells and the biomaterial ?

Scientific challenges in Tissue Engineering (Birla 2014, figure 1.6.) 2/2

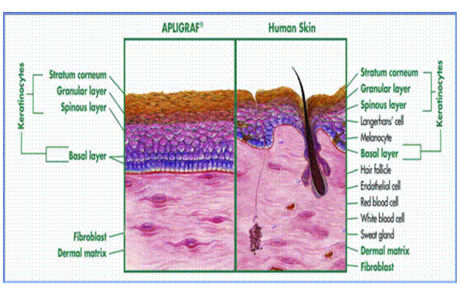
Embedded sensors	Bioreactors	Vascularization	In vitro assessment
Is real time monitoring of the tissue required ? What variables will be measured ?	What are the specific stimuli that guide tissue formation and function ?	How will vascularization be promoted within 3D Tissue ? How will this be perfused ?	Does the 3D integrate with the host tissue ? Are the cells migrating from the implanted tissue to the host ?

Example: Tissue engineered skin for wound healing – simple, but profitable

- http://www.organogenesis.com/news/media-materials/index.html



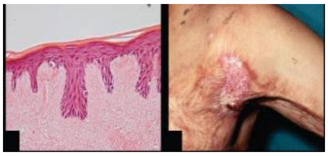
(http://www.organogenesis.com)



* http:// www.organogenesis.com

The clinical use of tissue-engineered skin

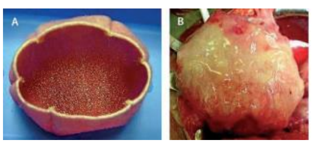
A. Patient's keratinocytes and fibroblasts are grown on the sterilized de-epidermized acellular donor dermis
B. Two months after the surgery



2007 Nature 445:874

Example: Engineering a tissue construct – getting more complicated, single patient applications in hospitals

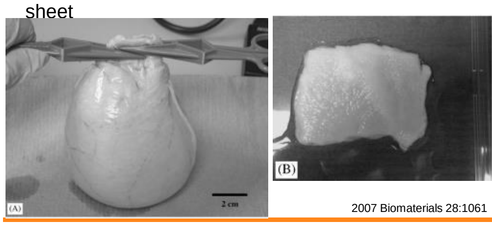
- Urothelial and muscle cells were isolated from patients.
- Cells were seeded on a biodegradable bladder-shaped scaffold made of collagen and polyglycolic acid.
- The cell-scaffold construct was connected to the native bladder in the patient.



2006 The Lancet (9518) 367:1241

Acellular bladder matrix for tissue engineering

A. The intact porcine bladder
B. The final decellularized bladder matrix as a flattened sheet



2007 Biomaterials 28:1061

Acelluration of human heart

- New technology to build heart constructs: https://www.youtube.com/watch?v=pd3TFB0wOI0